UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDE AND TOXIC SUBSTANCES

MEMORANDUM

Date: December 3, 2009

SUBJECT: Spirotetramat; Response to comments on human health effects submitted by Mayra Quirindongo of the NRDC

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I. CONCLUSIONS

Response to specific statements made by Mayra Quirindongo

I. In a recent submission to the Agency, Ms. Quirindongo of the Natural Resources Defense Council correctly noted that toxicity to the maternal animal was observed in the developmental toxicity study in the rabbit, while developmental toxicity was not observed in offspring at any dose up to the highest does tested, which was 4X higher than the dose at which maternal toxicity was observed. Therefore, offspring were actually less sensitive than maternal animal in the

developmental toxicity study in the rabbit. Ms. Quirindongo also correctly noted that in the remainder of the developmental and reproductive toxicity studies for spirotetramat, the LOAEL and NOAEL for offspring toxicity were the same as the LOAEL and NOAEL for parental toxicity, which indicates the absence of any quantitative susceptibility of offspring to spirotetramat. Ms. Quirindongo pointed out that the NOAEL was 6-12 times lower than the LOAEL in these studies, which was also the highest dose tested. Therefore, this dose spread indicates that the NOAELs are highly protective of any toxicity observed in offspring at the next dose up. In addition, the dose spread in these studies was not atypical; a similar spread can be cited for many other acceptable toxicity studies that have been conducted for pesticides and submitted for review to the Agency.

II. Ms. Quirindongo indicated that the EPA should have considered the severity of effects observed in the developmental and reproductive toxicity studies for spirotetramat. She notes that "Malformations and skeletal deviations – two of the endpoints in the rat developmental study – may lead to permanent disabilities in humans" (p. 4). However, the Agency is regulating at doses that are 100-200 times lower than the dose at which these effects were observed (the limit dose of 1000 mg/kg body weight/day) and then applying an additional 100-fold uncertainty factor on top of the selected point of departure, leading to a margin of exposure of 10,000-20,000. The Agency's assessment is, therefore, highly protective of the effects observed in both offspring and maternal animals at the limit dose in the rat developmental toxicity study.

III. On p. 4 of her submission, Ms. Quirindongo correctly points out that thyroid hormone levels were decreased in the one-year toxicity study in dogs. In the Agency's review of the toxicity database for spritotetramat, as well as in the peer review of the database that we conducted with our regulatory counterparts from Canada and Austria, we concluded that the decreased thyroid hormone levels observed in dogs were treatment-related. However, based on the absence of any corroborating signs of thyroid toxicity in the dog studies (including lack of decreased thyroid weight, lack of thyroid histopathology, lack of compensatory increases in TSH, lack of effect on UDP-glucuronosyltransferase activity, and the absence of any clinical signs of toxicity or changes in body weight that might result from decreased thyroid output), the decreased thyroid hormone levels were not considered adverse. In addition, it is noted that the NOAEL from the one-year toxicity study in dogs, which was chosen to calculate the chronic RfD, is below, and therefore protective of, the doses at which the statistically significantly lower, non-adverse, thyroid hormone levels were observed in this study.

IV. On p. 5 of her submission, Ms. Quirindongo notes that inhibition of the enzyme acetyl CoA carboxylase, which is the subcellular target of spirotetramat in insects, interferes with lipid biosynthesis. However, changes in plasma lipid parameters such as plasma triglycerides and plasma cholesterol, which should be indicative of disruption of lipid biosynthesis in mammals, were not observed in any animal study in the toxicology database for spirotetramat.

V. On p. 5 of her submission, Ms. Quirindongo correctly points out that spirotetramat does not have a neurotoxic mechanism of action in target insects and that spirotetramat is not considered a neurotoxic chemical in mammals. However, EPA does not agree with her statement that "male and female Wistar rats showed clinical signs of neurotoxicity" in the acute neurotoxicity study in the rat. The only clinical sign of toxicity observed in this study at any

dose was staining of the fur or perianal region with urine. Such staining is not a neurotoxic effect and was likely due to a colored metabolite that was excreted into the urine or feces or to a change in the pH of the urine due to an excreted metabolite. Although decreased motor activity was observed in the acute neurotoxicity study in the rat, there were no effects on movement or gait or any clinical signs of toxicity in the acute oral toxicity study in the rat at 10-fold higher doses (2000 mg/kg body weight). Therefore, since the findings in the acute neurotoxicity study in the rat were not corroborated by any other study in the database, they were consistent with the Agency's weight-of-the-evidence conclusion that spirotetramat is not a neurotoxic chemical.

Summary

Section 408(b)(2)(C) of FFDCA provides that EPA shall apply an additional tenfold (10X) margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the database on toxicity and exposure unless EPA determines based on reliable data that a different margin of safety will be safe for infants and children. This additional margin of safety is commonly referred to as the FQPA SF. In applying this provision, EPA either retains the default value of 10X, or uses a different additional safety factor when reliable data available to EPA support the choice of a different factor.

As stated in the Federal Register for July 9, 2008 (Volume 73, Number 132), EPA determined that reliable data show that the safety of infants and children would be adequately protected if the FQPA SF were reduced to 1X for spirotetramat. That decision was based on the following findings in the toxicity and exposure databases:

1. Offspring were less sensitive (not more) than maternal animals in the developmental toxicity study in the rabbit.

2. There was no evidence that offspring were more sensitive than parental animals following the pre- or postnatal exposure of rats (i.e., in the prenatal developmental study or in the 2-generation reproduction study).

3. There was no indication that spirotetramat was a neurotoxic chemical. Clinical signs of toxicity and decreased motor activity were observed in adult rats following a single dose of spirotetramat in the acute neurotoxicity study in the rat; however, these effects only attained statistical significance at high doses and were not observed at the limit dose in, and therefore were not corroborated by, the acute oral toxicity study in the rat. Because a clear NOAEL was attained in the acute neurotoxicity study, the use of this study to calculate the acute RfD is considered protective of all relevant populations including infants and children.

4. There was no concern for neurotoxicity with spirotetramat in the developing animal. Evidence of toxicity to the developing nervous system was not found in any of four developmental or reproductive toxicity studies with spirotetramat. Brain dilation observed in the one-year dog study was considered to be most likely a congenital anomaly with a high spontaneous occurrence. This finding was not observed in any other study in the spirotetramat database.

5. The compounds spirodiclofen and spiromesifen, which are structurally related to spirotetramat, are not neurotoxic in adults or young.

6. There was no need for a developmental neurotoxicity study or additional uncertainty factors to account for neurotoxicity.

7. There were no residual uncertainties identified in the exposure databases. The dietary food exposure assessments were performed based on 100% crop treated and tolerance-level residues. EPA made conservative (protective) assumptions in the ground water and surface water modeling used to assess exposure to spirotetramat in drinking water. These assessments will not underestimate the exposure and risks posed by spirotetramat.

8. There were no registered or proposed uses of spirotetramat which could result in residential exposure to infants and children.

II. ACTION REQUESTED

Please address the comments made by NRDC regarding human health for spirotetramat.